REMARKS

I. Introduction

Receipt is acknowledged of the Final Office Action mailed March 11, 2004. In response to the Examiner's restriction requirement, claims 1, 11, and 12 were elected. Claims 2-20 and 13-24 have been canceled without prejudice or disclaimer. Claims 25-26 have been added to claim aspects of the invention. Claims 1, 11, and 12 have been amended to correct informalities. Support for amended claim 1 may be found at page 4, paragraphs 6-7 to page 5, first paragraph, and the bottom of page 6 of the specification. Support for new claim 25 may be found at pages 3-4 of the specification. Support for new claim 26 may be found at page 6, paragraph 2 of the specification. No new matter has been added by these amendments.

Applicants thank the Examiner for withdrawing the previous objection to the term "derived" in the Office Action of August 1, 2003.

II. Applicants' Response to the Examiner's Rejections

A. Non-Elected Subject Matter

The Examiner has withdrawn Applicants' new claims 23 and 24 from consideration as being directed to a non-elected invention under 37 CFR § 1.142(b). The Examiner has alleged that because Applicants elected Group II, a composition comprising a combination of a single human non-cancerous prostate cell line, PNT-2, a cancerous prostate cell line, LNCaP, and a primary prostate cell line, NIH-1542, for action on the merits, claims 23 and 24 constitute non-elected subject matter.

Applicants respectfully traverse this rejection on the basis that the second grouping specifically allows for one, two, or three cell lines that are derived from non-cancerous tissues

(page 4, last paragraph-page 5, first paragraph of the specification). Nevertheless, without acquiescing in this rejection, Applicants have canceled claims 23 and 24, as the Examiner has suggested, and amended claim 1 to recite "An allogeneic immunotherapeutic agent for the treatment of prostate cancer comprising three human prostate cell lines from three different sources, wherein said sources are selected from the group consisting of: (a) normal prostate human tissue, (b) primary prostate human tissue, and (c) metastatic prostate human tissue, and wherein one or more of said human prostate cell lines is non-cancerous". Applicants respectfully submit that the cancellation of claims 23 and 24 and amendment of claim 1 render this rejection moot, and this rejection should be withdrawn.

B. Rejections Under 35 USC § 112, first paragraph

1. Written Description

The Examiner has rejected claims 1, 11, and 12 under 35 USC § 112, first paragraph, on the grounds that the specification does not contain a written description or any clear support of the limitation of "at least one human prostate cell line is non-cancerous " in the claimed invention or the claims as originally filed.

Applicants respectfully traverse this rejection, and without acquiescing in this rejection, Applicants note that the Examiner is correct that the specification discloses support for a vaccine which may be based on one *or a combination* of different immortalized normal cells derived from the prostate (p.4, paragraph before last) (emphasis added). An immortalized normal cell is derived from normal human cells that seem to be normal in all respects (i.e., they would not be classified as pathological by a skilled histopathologist). Applicants also note that "a further aspect of the invention is the addition of TSAs and/or TAAs by combining *one or more immortalized normal*

cell line(s) with one, two, or three different cell lines derived from primary or metastatic cancer biopsies" (page 4, last paragraph-page 5 of the specification) (emphasis added). Nevertheless, in view of Applicants' election of the species, Applicants have amended claim 1 to recite: "An allogeneic immunotherapeutic agent for the treatment of prostate cancer comprising three human prostate cell lines from three different sources, wherein said sources are selected from the group consisting of: (a) normal prostate human tissue, (b) primary prostate human tissue, and (c) metastatic prostate human tissue, and wherein one or more of said human prostate cell lines is non-cancerous" in order to clarify the claimed invention.

Applicants respectfully submit that this amendment renders this rejection moot, and this rejection should be withdrawn.

2. Enablement

At pages 3-7 of the Office Action, the Examiner has maintained the rejection of claims 1, 11, and 12 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure for the reasons of record in the Office Action of August 1, 2003. The Examiner has maintained that allegedly 1) no data has been submitted that illustrates the general principle that the use of an immortalized normal cell line can be applied across *many different tumors* and 2) there is no data showing that *human prostate cancer* is effectively treated by *human prostate cell lines*, in view of the alleged fact that cancer treatment is unpredictable, as taught by Gura *et al.*, Jain *et al.*, Curti *et al.*, and Hartwell *et al.*

Applicants respectfully traverse this rejection, and without acquiescing in the rejection, Applicants note that concerning the intertwined issues of enablement and utility:

> [I]t follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the inventor's asserted utility. * * * Taking these facts the nature of the invention and the PTO's proffered evidence into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO has not satisfied its initial burden. ***Accordingly, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112.***

In re Brana, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (emphasis added), *citing In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971). The burden of establishing a Section 112 enablement rejection rests with the Examiner. *See* MPEP §§ 2164.02 at 2100-181; 2164.04 at 2100-183 (Rev. 1, February 2003). Applicants respectfully submit that the Examiner has not met this burden. Accordingly, Applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *Id.* The "Utility Guidelines" pursuant to MPEP § 706.03(a)(1)(B)(1) instruct an Examiner that, "[i]f the applicant has asserted that the claimed invention is useful for any particular purposes (*i.e.* a 'specific utility') and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." *See* Utility Examination Guidelines, 66 Fed. Reg. 1092 (January 5, 2001). The same holds true for enablement rejections related thereto as per *Brana*. Nevertheless, Applicants explain below why the claims are enabled by the specification.

a. Applicants' Phase I Human and Mouse Data is Sufficient for Patentability

Applicants respectfully submit that the Phase I human and mouse data submitted in the instant application and the Walker Declaration is sufficient for patentability purposes to establish enablement of the claimed prostate cell lines in the treatment of prostate cell cancer in mammals. Applicants would like to remind the Examiner that the requirements under the law for obtaining a patent and the requirements for obtaining government approval to market therapeutic agents for human consumption are different. *See Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). "Testing for the full safety and effectiveness of a [therapeutic agent] is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings." *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

b. The Use of Immortalized Normal Cell Lines Can be Applied Across Different Types of Tumors

In response to the Examiner's assertion that *no* data has been submitted that illustrates the general principle that the use of an immortalized normal cell line can be applied across *many different tumors*, Applicants respectfully traverse this rejection and point out that the term "many" is vague and represents an indeterminate amount of tumors. "There is no magical relationship between the number of representable examples and the breadth of the claims with respect to enablement, and compliance with § 112, first paragraph, does not turn on whether a specific example is disclosed." *In re Colianni*, 561 F.2d 220, 195 USPQ 150 (CCPA 1977); *see also* MPEP § 2164.03. Applicants are not attempting to claim the treatment of an indeterminate amount of tumors or even *many different types of tumors*. Rather, Applicants' claim 1 is directed

to the treatment of *prostate* tumors.

Nevertheless, Applicants submit that the several examples in the specification and the Walker Declaration are sufficient for illustration purposes to show that cell lines may be used as cancer vaccines to treat *several other* different types of tumors. Applicants have provided data relating to the use of immortalized normal cell lines to treat patients with three types of tumors. The first set of data involves the treatment of human *prostate* tumors (*see* page 6, second paragraph and the table labeled "cell lines administered" in the specification) and mouse *prostate* tumors (*see* Experiment 3, Onyvax R&D #3 in Appendix C of the Walker Declaration). The table on page 6 lists several immortalized cell lines such as PNT-2 and NIH-1542. Applicants have also provided data showing the use of an immortalized normal cell line to treat *melanoma* tumors in mice (*see* Experiment 2, Onyvax R&D #1 in Appendix C of the Walker Declaration). Finally, Applicants have provided data showing the results of using an immortalized normal cell line to treat *renal* tumors in mice (*see* Experiment 4, Onyvax R&D #3 in Appendix C of the Walker Declaration). To require Applicants to show any more examples relating to the use of cell lines to treat *many different types of tumors* would place an undue burden on the Applicant.

c. Results from Treatment of Cell-Based Vaccines of Other Types of Cancer Can be Extrapolated to Prostate Cancer

The Examiner has alleged at page 7 of the Office Action that one cannot extrapolate the results of treatment of other cancers, such as melanoma, to treatment of prostate cancer, because the type and degree of antigenic stimulus by other cancers such as melanoma cells relevant to cancer cell growth are not necessarily similar to those of prostate cells because of differences in etiology and different responses to therapeutic agents.

Applicants do not understand the point being made by the Examiner given the Examiner's previous concerns about immortalized cell lines being employed against many cancer types.

d. Mouse Model Prostate Cancer Data May be Extrapolated to Human Prostate Cancer

The Examiner has alleged at page 7 of the Office Action that in the absence of objective evidence, the Applicants have not shown that non-cancerous prostate cell lines can be used to effectively treat mouse prostate cancer or that the mouse model disclosed by the Applicant is representative of human prostate cancer, because it is allegedly well known in the art that human prostate cancer is a very slow type of cancer, whereas mouse prostate cancer does not have the same characteristics or properties of human prostate cancer.

Applicants respectfully submit that the data in the specification and the Walker declaration shows the effective treatment of mouse prostate cancer using non-cancerous prostate cell lines. For example, Experiment 3 (Onyvax R&D #2) at page 2 of the Walker Declaration, under "results and conclusions," states that the use of a mouse non-cancerous prostate cell line to treat prostate cancer cells in mice "shows significant efficacy of the normal cell line as immunotherapy". Examiners are reminded that they must treat as true credible statements made by an applicant or a declarant in the specification or in a declaration provided under 37 CFR § 1.132, unless they can show that one of ordinary skill in the art would have a rational basis to doubt the truth of such statements. 60 Fed. Reg. 97 (Jan. 3, 1995). Thus, not accepting the opinion of a qualified expert that is based on an appropriate factual record would clearly be improper. *Id.* Courts have upheld these guidelines. In *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), the applicants provided a declaration including test results showing that several compounds within the scope of

the claims exhibited significant anti-tumor activity against their standard tumor model *in vivo*. The court held that "such evidence alone should have been sufficient to satisfy applicants' burden." *Id.*

The instant rejection is also similar to that encountered by the Court of Customs and Patent Appeals in *In re Isaacs*, 146 USPQ 193 (CCPA 1965). In the *Isaacs* case, the Examiner stated that the *in vivo* data was necessary to prove the utility of an anti-viral compound, even if the utility is believable. *See Isaacs*, 146 USPQ at 195. In rejecting this approach to examination, the Court explained that "It is our opinion that the instant disclosure would satisfy one of ordinary skill in this particular art that the claimed invention possesses the alleged utility. Even more to the point, however, it seems manifestly clear from the record that the alleged utility is *not* "incredible in light of the knowledge of the art, or factually misleading." In such a case it is clearly improper for the Examiner to make a demand for further test data, which as evidence would be essentially redundant and would seem to serve for nothing except perhaps to unduly burden the applicant. *In re Isaacs*, 146 USPQ 193, 196 (CCPA 1965) (emphasis in original).

With regard to the mouse data, Applicants submit that this data is sufficiently predictive of the results that would be obtained with other mammals, including humans, and thus the rejection cannot be sustained. *See* MPEP § 2164.02 at 2100-181 (Rev. 1, February 2003) (stating that a rigorous or exact correlation is not required). Applicants submit that mouse data would even be considered a rigorous correlation to human data, and the only type of data that would be closer is human data itself. But MPEP § 2107.03 at page 2100-45 (Rev. 1, February 2003) explains that applicants should not be required to provide human clinical data to obtain a patent.

Applicants also respectfully submit that the data disclosed in the specification and the

Walker Declaration disclosing the use of claimed cell lines to treat prostate cancer in mice is sufficient to establish the same enablement and utility in humans. Applicants remind the Examiner that the majority of the data in the originally-file specification shows the use of the claimed prostate cell lines in humans patients (page 6, paragraph 3 of the specification; Example 1; Figures 1-4). Although the mice disclosed in the specification and Walker Declaration do not have prostate cancer *per se* (page 12 of the specification; experiments 2-4 in Appendix C of the Walker Declaration), it is well-known in the art that experimental results involving mice with artificially-induced prostate cancer may be extrapolated to humans. In *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), the court held that the applicants' application for a pharmaceutical composition to treat cancerous tumors satisfied the enablement requirement of 35 USC § 112 since the specification implicitly asserted that the claimed compounds were highly effective against tumor models in which mice were injected with cell lines representing specific lymphocytic tumors. The Commissioner contended, however, that the cell lines were not diseases since the only way an animal could get sick was by a direct injection of the cell line. The court disagreed and pointed out that the cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the cell lines represented actual specific lymphocytic tumors which would produce this particular disease once implanted in mice. The court found that if applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo*, there would be no effective way to test compounds *in vivo* on a large scale. *Id.* Thus, courts have recognized that it is commercially, as well as scientifically advantageous to extrapolate experimental animal results to humans.

In contrast to the Examiner's assertion that the extrapolation of murine prostate tumor models to human prostate tumors is "questionable" because the rate of growth of prostate cancer in mice is allegedly "much slower than in humans", Applicants submit that there are similarities that outweigh the alleged differences between mice and human prostate cancer models. Humans and mice are both mammals. Also, the "slow, temporal development of increasingly severe preneoplastic lesions" associated with prostate cancer in mice is "remarkably restricted to the prostate gland, a property similar to the aging related progression of these lesions in humans".[1] Further, according to the National Cancer Institute, "[f]or a variety of reasons, mice are particularly well suited for cancer research. To start, mice and humans are similar in their genetic makeup and susceptibility to cancer. As a result, the development of tumors in mice largely parallels that in humans. Further, mouse tumors develop over the course of months rather than the years usually required for cancer to develop in larger animals and humans."[2]

Courts have acknowledged the necessity and utility of extrapolating results from experimental cancer treatment of animals to humans. The court in *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), held that the Patent and Trademark Office improperly rejected, for lack of utility, the applicants' claims for pharmaceutical compounds used in cancer treatment in humans. *Id.* The court held that even if the utility of the compounds could be reasonably questioned, evidence that the compounds were within scope of the claims, and other structurally similar compounds were effective as chemotherapeutic agents in *animals*, would be sufficient to convince one skilled in the art of their asserted utility. *Id.* (emphasis added). Absence of evidence

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[1] Powell et al., *Current Drug Targets*, Vol. 4, No. 3, April 2003, pp. 263-279.

[2] http://plan2003.cancer.gov/about/mmhcc.htm.

that the claimed compounds had a chemotherapeutic effect in humans did not warrant a contrary conclusion, since proof of the alleged pharmaceutical properties for such compounds by statistically significant tests using standard experimental animals was sufficient to establish utility. *Id.* Other courts have extended this approach to conclude that any *in vitro* test results can raise a presumption of *in vivo* usefulness of cell lines as a cancer treatment. *Ex parte Hirsch*, 34 PTCJ 588 (BPAI 1987). *See also* MPEP § 2164.02 (Rev. 1, February 2003) (supporting the use of *in vitro* data to support patentability).

For these reasons, Applicants submit that it is scientifically, commercially, and legally sound to extrapolate the mouse model prostate cancer treatment results disclosed in the instant application to human prostate cancer.

e. Human Prostate Cancer Can be Effectively Treated with Human Prostate Cell Lines

Treating cancer does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995, *citing In re Jolles*, 628 F.2d at 1327, 206 USPQ at 890. Modern science has previously identified numerous successful chemotherapeutic agents. *Id.* Morton *et al.* (WO 91/06866), *supra*, teach that "significant progress has been made in developing assays using tumor markers, including ..., e.g., CEA, alpha-fetoprotein, [and] *prostate specific antigen*, etc. (p. 9, first paragraph of WO 91/06866) (page 4, second paragraph of the specification) (emphasis added).

In response to the Examiner's reliance on Gura *et al.*, Jain *et al.*, Curti *et al.*, and Hartwell *et al.*, Applicants note that these references were published in 1997, 1994, 1993, and 1997, respectively. Between 7 to 11 years have passed between now and the date that these articles were

published, and between 2 and 6 years have passed since Applicants' earliest filing date of December 9, 1999. Applicants submit that these references are outdated regarding whether cancer therapy would be predictable or not. The technology of cancer therapy and treatments changes at such a fast rate that a reference of even a few years ago could be irrelevant because of new developments in the art. Furthermore, Gura *et al.*, Jain *et al.*, Curti *et al.*, and Hartwell *et al.* teach that it is difficult to develop safe, effective anti-cancer drugs, in contrast to the claimed invention which is directed to anti-cancer cell lines.

Applicants point out that all of the cell lines PNT-2, NIH-1542, and LnCap[3] of the claimed invention were derived from human prostates (*See* Experiment 1, Phase I trial, "Vaccine Cell Lines Used to Treat Subjects" column, p. 1 of the Walker Declaration). The results of Experiment 1 are shown in Figures 1, 2, and 3 of the specification. Figure 1 shows the T-cell proliferative data response for patients 112, 307, and 406 after being treated with human prostate cell lines PNT-2, NIH-1542, and LnCap. Figure 2 shows Western Blot analysis of serum from patients 115, 304, and 402. Figure 3 shows prostate specific antigen (PSA) data for patients 110, 303, and 404. Overall, 50% of the patients treated with the cell lines PNT-2, NIH-1542, and LnCap mounted a specific proliferative response to at least one of the human prostate cell lines. Applicants submit that a 50% response rate is sufficient to indicate an "effective treatment" of human prostate cancer using the claimed human prostate cell lines.

[3] ATCC Nos. CRL-1740 and 1740D, from the prostate of *homo sapiens*.

f. A T Cell Immune Response is a Sufficient Indication of Effective Prostate Cancer Treatment Using Human Prostate Cell Lines

The Examiner has alleged at page 5 of the Office Action that in view of Boon, even if a T cell immune response or an increase in activated CTLs is elicited in prostate cancer patients, one cannot predict whether this immune response would be effective for treating cancer due to inconsistencies in antigen expression or presentation by tumor cells, and in order to get active immunization in human patients, it would be necessary to stimulate immune defenses of organisms that have often carried a *large tumor burden*, which may have established an immune tolerance and could prevent immunization.

Applicants respectfully traverse this rejection and without acquiescing in the rejection, Applicants explain that antigen expression or presentation by tumor cells is not inconsistent. It is well-known in the art that immune responses mediated by T cells play a critical role against tumors. Boon teaches at page 178, second paragraph that "*most if not all* rodent tumors express antigens that can mediate immune elimination ...." (emphasis added). If antigen expression or presentation were inconsistent, a much smaller percentage of rodent tumors would mediate immune elimination. Boon further teaches that the "T cell receptor binds to a small antigenic peptide located in a groove of the MHC molecule [which is] ... known with a remarkable degree of precision both for mouse ... and for humans." (p. 179, paragraphs 2 and 3). If such binding properties of antigen-presenting molecules are so precise, it is hard to understand why antigen presentation would be inconsistent. Boon also teaches at page 184, paragraph 3 that antigens are "specific for each variant" derived from the same tumor cell line and at page 185, last paragraph that "antigens defined by CTLs were responsible for the immune rejection of ... [these] variants". At page 194, Boon teaches that " an elaborate presentation mechanism" is conferred upon T

lymphocytes. In view of such elaboration and precision of antigen specificity and presentation, it is unlikely that T cell responses or antigen presentation are inconsistent. Even if T cell responses or increased CTLs were inconsistent, because CTL responses are "not always essential for rejection," and "depend entirely on the nature of the initial tumor" (page 187, paragraph 1), a lack of T cell response or increase in CTLs would not negate a prediction as to whether an immune response was indicative of effective prostate cancer treatment because while prostate cancer tumors are different from other types of tumors, as mentioned above, antigens show different specificities for different types of tumors, including prostate tumors.

Applicants respectfully submit that large tumor burdens are less relevant in prostate cancer where tumor volumes are usually low except in very terminal stages, and that the size of a prior prostate tumor burden in a human, if present, should not matter when extrapolating the results of mouse model prostate cancer treatments to human prostate cancer treatment models. Martin *et al.* (*Math Biosci.*, 110(2):201-19, 1992) evaluated three different types of tumor growth and found that for exponential and logistic tumor growth, the tumor burden during therapy is shown to have little impact upon survival time. When the tumor was in Gompertz growth, therapies maintaining a large tumor burden doubled and sometimes tripled the survival time under aggressive therapies aiming for a rapid reduction in the sensitive cell subpopulation. *Id.* Martin *et al.* concluded that since treatments maintaining a high tumor burden are optimal for all three types of tumor growth, it may no longer be necessary to know the growth characteristics of a tumor to schedule anticancer drugs. *Id.* Thus, the size of a prior tumor burden in a human is of negligible concern when comparing mouse to human prostate cancer treatment results, and may even be optimal for cancer treatment.

g. A Decrease in PSA Level is an Indication of Effective Prostate Cancer Treatment

The Examiner has further alleged that while the presence of prostate cancer may be indicated by increased PSA levels, a decreased PSA level does not necessarily indicate effective treatment of prostate cancer using the claimed prostate cancer cell lines. The Examiner has alleged that this is because the decreased level of PSA could be attributed to other events, such as the induction of antibodies produced by the administered prostate cancer cell lines that produce PSA, or because such cell lines have PSA on their cell surface. Thus, the Examiner has alleged that one cannot assess whether a reduction in PSA level is due to an induced production of anti-PSA antibodies or a reduction in the growth of prostate cancer cells.

Applicants respectfully traverse this rejection and point out that Figure 3 of the specification clearly shows that the decrease in PSA levels are due to the treatment of the three prostate cell lines PNT-2, NIH-1542, and LnCap. Reduced PSA levels cannot be attributed to an anti-PSA antibody response with subsequent removal of the antibody/PSA complex or to PSA on the surface of prostate cell lines because the antibodies may sometimes have an immune response to themselves, thereby abrogating their activity, or they may be unable to access the tumor lesion through the blood vessels.

Furthermore, very few remedies have been proven to decrease PSA levels (i.e., drugs or surgical procedures). Hence, Applicants' invention serves a long-felt need for less chemically toxic or invasive therapeutic agents to treat prostate cancer. The measurement of PSA levels is still widely-used and accepted as a tumor marker for prostate cancer. Scher *et al.*, *J. Clin. Oncol.*, 22:3, pp. 537-556, 2004, teach that "no tumor marker has had as great an impact on the diagnosis

and management of a disease as has PSA level in prostate cancer" (p. 538, left col., 1st paragraph). Agents which fail to affect PSA kinetics are not considered useful therapeutic candidates, whereas a favorable impact on PSA kinetics indicates potential treatment effects and clinical benefits (Sher et al., p. 551, col. 1, middle section). Decreases in PSA levels as an indicator of effective treatment of prostate cancer have been used to justify large investment decisions aimed at proving clinical efficacy (p. 544, right col., last paragraph). Thus, PSA kinetics should be considered as giving an indication of a therapeutic effect on prostate cancer in the absence of evidence to the contrary.

In view of the above remarks, Applicants respectfully submit that the Examiner has not established why the claimed invention would not possess those characteristics that would be effective in treating prostate cancer in mammals and humans. Accordingly, Applicants respectfully submit that the rejection has not met the burden of establishing a *prima facie* case of non-enablement since the rejection has not demonstrated why the claimed invention would not work to treat prostate tumors in mammals and humans. Applicants therefore submit that claims 1, 11, and 12 are adequately enabled. Accordingly, reconsideration and withdrawal of the rejections under § 112, first paragraph is respectfully requested.

2. Scope

The Examiner has maintained the rejection of claims 1, 11, and 12 under 35 U.S.C. § 112, first paragraph, at pages 7-9 of the Office Action for the same reasons of record in the Office Action of August 1, 2003. The Examiner has alleged that there is a lack of enablement for an allogeneic immunotherapeutic agent for the treatment of prostate cancer comprising at least one of

"any" non-cancerous human prostate cell lines or for an allogeneic immunotherapeutic agent for the treatment of prostate cancer comprising "alive" cancerous human prostate cell lines.

Applicants respectfully traverse this rejection and point out that it is the Examiner's burden to provide a reason to doubt the efficacy of any cell line, and Applicants respectfully submit that the Examiner has not done so. As pointed out previously, Applicants have provided several examples showing that the claimed cell lines are effective for treating prostate cancer.

Nevertheless, without acquiescing in this rejection, Applicants submit that this rejection has been rendered moot by amended claim 1 which recites: "An allogeneic immunotherapeutic agent for the treatment of prostate cancer comprising three human prostate cell lines from three different sources, wherein said sources are selected from the group consisting of: (a) normal prostate human tissue, (b) primary prostate human tissue, and (c) metastatic prostate human tissue, and wherein one or more of said human prostate cell lines is non-cancerous." While amended claim 1 narrows the breadth from "any" human prostate cell line to cell lines derived from specific types of tissue, Applicants point out that in the context of the present invention, the Examiner's contention that few human prostate cell lines have been established is not dispositive. What is important is using cells from different cell lines, in order to expose the patient to many tumor associated antigens (TAA) and tumor specific antigens (TSA) that are expressed by the combination of cell line types. This approach enhances mismatch of haplotype and maximizes allogenic potential and the subsequent immune response to the product.[4] Because the claimed vaccine cells, comprising the cell lines PNT-2, NIH-1542, and LnCap, are genetically and

[4] Positive T-cell proliferation data are set forth in Figure 1 and page 6 of Applicants' specification, and positive PSA data are set forth in Figure 4 and page 11 of Applicants' specification.

immunologically mismatched to the haplotype of the patient being treated, they will be rejected and will not cause cancer in that patient. (*see* pages 3-4 of Applicants' specification). In view of this, Applicants have added new claim 25 which recites: " The allogeneic immunotherapeutic agent of claim 1, wherein said cell lines are selected so as to maximize haplotype mismatch." Applicants have also added new claim 26 to recite " The allogeneic immunotherapeutic agent of claim 1, wherein said cell lines derived from primary and metastatic prostate human tissue are rendered replication-incompetent by irradiation" to distinguish the claimed invention so that it does not comprise "alive" cancerous human prostate cell lines.

With regard to the Examiner's citation of experiments in mice, it is well-known in the art that the purpose of using mice in cancer research is to provide a model involving xenographic rejection. Applicants submit that the animal studies cited by the Examiner are in mice that have been designed not to reject human tumors. Wu *et al.* teach a bone xenograft model for prostate cancer cells in intact athymic or SCID/bg mice (p. 892). Triest *et al.* teach a metastatic prostate carcinoma using a xenograft tumor model in Balb/c mice (athymic), which will not reject human tumor cells. Similarly, the mice used in experimentation are useful because they do not reject human tumor cells, but do not indicate that the administered cells can cause cancer in patients receiving treatment.

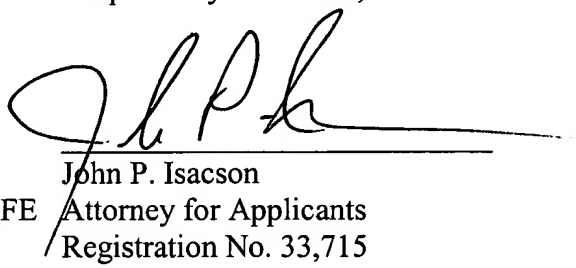
Therefore, Applicants respectfully request withdrawal of the scope rejection of claims 1, 11, and 12 under 35 U.S.C. § 112, first paragraph.

III. Conclusion

In light of the above remarks and arguments, Applicants respectfully request that all objections and rejections be withdrawn and that a timely Notice of Allowance be issued in this application. Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

June 7, 2004
Date



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